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Weight loss and weight loss maintenance efficacy of a novel weight loss program: The retrospective RNPC® cohort

Tanja K. Thorning[a], Odile Fabre[b], Rémy Legrand[b], Arne Astrup[a], Mads F. Hjorth[a,*]

[a] Rolighedsvej 26, 1958, Frederiksberg C, Department of Nutrition, Exercise and Sports, University of Copenhagen, Denmark
[b] Groupe Éthique et Santé, Actiburo 1, Bâtiment A, 100 Chemin de L'Aumône Vieille, 13400 Aubagne, France

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ABSTRACT

Objective: Bodyweight loss is essential to lower risk factors for type 2 diabetes and cardiovascular disease in overweight patients. Therefore, we examined the effectiveness of the RNPC® program for short and long term bodyweight reduction.

Methods: The RNPC® program is a novel weight loss and maintenance program achieving weight loss by an energy-restricted 800–1000 kcal/day high-protein low-glycemic diet (weight loss phase), followed by an intensive follow-up with a step-wise increase in energy intake to reach energy balance (weight stabilization phases). The analysis included 12,179 overweight or obese patients treated in 54 RNPC® weight loss clinics in France.

Results: A total of 10,809 (89%) patients completed the initial weight loss phase and 2996 (25%) completed the full program. Median weight loss percentage was 10.7% (Interquartile range [IQR]: 5.8; 16.5) after a median of 105 days (IQR: 56; 175) during the weight loss phase, and a median of 17.5% (IQR: 12.7; 24.2) after a median of 251 days (IQR: 187; 350) at program completion.

Conclusion: The RNPC® program is cost-effective and well tolerated for short-term body weight loss as well as effective in the long term among the patients completing the program. The program might be particularly effective among patient with elevated fasting glucose.

What is already known about this subject

- High-protein diets are preferred for weight loss and weight loss maintenance.
- An initial large and rapid weight loss is a determinant of long-term weight maintenance success.
- Losing weight is difficult but long-term weight loss maintenance is even more difficult.

What this study adds

- The RNPC® program is cost-effective compared to other programs and pharmaceuticals.
- The RNPC® program is well tolerated for short-term body weight loss as well as effective in the long term among the patients completing the program.
- The program was more effective among patients with elevated fasting plasma glucose although likely to have been confounded by baseline body size.

1. Introduction

Overweight and obesity are a global health problem, and the number of adults with obesity has doubled since the 1980's. Globally, 39% of adults were overweight and 13% were obese in 2014 (WHO, 2017). Overweight and obesity account for almost half of the global burden of diabetes and more than a fifth of ischemic heart diseases (WHO, 2009). A 5–10% weight loss is linked to clinically relevant reductions in risk factors for diabetes and cardiovascular diseases. Therefore, for individuals with overweight or obesity or those at high risk of developing obesity and its comorbidities, the World Health Organization points toward the need for initiatives and health professionals with expertise in obesity management. This should support prevention of weight gain, help promotion of weight maintenance, support management of obesity comorbidities and promote weight loss (WHO, 2000). Several more or less efficient weight loss programs have been designed for achievement of weight loss (Gudzune et al., 2015), however, with less focus on the weight loss maintenance. Weight regain typically occurs after weight loss (Sacks et al., 2009; Larsen et al.,

* Corresponding author. Rolighedsvej 26, 1958, Frederiksberg C, Department of Nutrition, Exercise and Sports, University of Copenhagen, Denmark.
E-mail address: madsfiil@nexs.ku.dk (M.F. Hjorth).

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2010), and after a weight loss ≥10% of initial body weight, only about 20% succeed in maintaining weight loss over the long term (> 1y) (Wing and Phelan, 2005). The optimal diet composition for body weight management is still being debated; however, some diets seem to be better than others in terms of controlling appetite and reducing weight regain. According to results from the pan-European Diogenes study, that investigated weight loss maintenance with *ad libitum* diets in four combinations of low and high protein, and low and high GI or a control diet, the combination of high protein and low GI was the most successful diet for weight loss maintenance (Larsen et al., 2010). Protein is regarded as the most satiating macronutrient per calorie, and a dose-response relationship between protein content of the diet and subjective feelings of satiety has previously been shown (Belza et al., 2013). Earlier, a high-protein diet was also shown to induce a larger weight loss than a high-carbohydrate diet (Skov et al., 1999), and a high weight loss is preferable, as larger weight reduction during a weight loss intervention is a predictor for successful long-term weight maintenance (Sawamoto et al., 2017; Unick et al., 2014). Furthermore, the odds of regaining weight decrease the longer the weight loss is maintained, and individuals who maintain weight loss longer > 2y reduce their risk of subsequent regain by ~50% (Wing and Phelan, 2005).

The aim of the present study was retrospectively to examine the effectiveness of the RNPC® program – a novel dietary approach carried out at 54 centers in France - for short and long-term reduction of body weight, fat mass and waist circumference. Secondarily, possible pre-treatment determinants of successful weight loss and weight maintenance among the RNPC® patients were investigated.

2. Materials and methods

2.1. Design

The RNPC® program (for Rééducation Nutritionnelle Psycho-Comportementale, *i.e.* Nutritional Psycho-Behavioural Reeducation). is a novel ongoing weight loss program managed by 54 RNPC® centers distributed across France. The concept of the RNPC® program is a three-phase weight loss and weight loss maintenance program (Supplementary Fig. 1). During the entire program, frequent measurements and nutritional consultations of patients are carried out every second week at the RNPC® center with a trained dietician. The frequent visits were ensured by providing the patient only with the number of RNPC® meal supplements needed until next visit. The program starts with a weight loss phase where a rapid weight loss is achieved. The patient determines his target weight loss in agreement with the dietician and the physician. When the objective is reached, the weight loss phase is followed by a weight stabilization phase, during which energy intake is gradually increased in five steps. Between each of the five steps of the stabilization phase, energy intake is increased according to the calculation: next energy level = previous energy level + (post-weight loss energy requirement – weight loss energy intake)/5. Post-weight loss energy requirement was determined by the Black's formula (Black et al., 1996) using a sedentary physical activity level of 1.375. The program ends with a weight maintenance phase where energy intake matches the post-weight loss energy requirement, thereby energy balance is achieved. In the weight-maintenance phase no RNPC® meal supplements are consumed, and consultations with the RNPC® dietician are optional, but offered as long as the patient's wishes this support. The phases of the RNPC® program are designed to be of individual-specific time-duration depending on the size of the achieved weight loss. For each one kg body weight lost during the initial weight loss period, one week is added to the weight stabilization phase. For example, a person achieving a 15-kg weight loss during the weight loss phase would have three weeks in each of the five steps in the stabilization phase, thus a total of 15 weeks in the stabilization phase, before entering the weight maintenance phase. The RNPC® program was designed to be very dynamic and manageable in real life, in order to support the patients in completing the program and hence achieving weight loss and weight loss maintenance. Therefore, in case of weight regain during the program, the patients were allowed to relapse to an earlier energy level of their program. Also, more than one weight-loss phase could take place if needed, and patients could participate in the program more than once.

2.2. Diet

The RNPC® weight loss diet is composed of daily intake of vegetables, animal protein (from meat, fish, eggs or shellfish), and commercially available meal supplements in the form of snacks (biscuits, cereal bars, bread, crackers, soups, omelets, drinks and desserts) which the patients can eat whenever they want. The weight loss diet targets an energy intake of 800 kcal/day in women and 1000 kcal/day in men, and a macronutrient composition of 60% proteins (1.5 g/kg in men and 1.2 g/kg in women), 25% low-GI carbohydrates, and 15% fat. The RNPC® meal supplements were selected to support a high level of high-quality proteins (containing an average of 110 kcal, 15.8 g proteins, 2.4 g carbohydrates, 5.4 g fats and 2.3 g fibers, for an average serving size of 30 g) in the diet and these were fortified with vitamins and minerals in order to avoid deficiencies caused by a low energy intake. Also, the products comply with the requirements specified by the European Food Safety Authority (EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2015). During the weight loss phase, the RNPC® meal supplements contribute approximately 40% of the total energy intake. During the weight stabilization phases of the RNPC® program, the intake of meal supplements gradually decreases as the patients' normal diet was reintroduced by the dieticians; however, with increased focus on dietary sources of high-quality proteins. Energy percentage from dietary proteins is gradually decreased during the course of the weight stabilization phase, and targeted a macronutrient composition of 25% proteins, 45% carbohydrates and 30% fats at the transition to the weight maintenance phase, i.e. completion of the program. The diets throughout the program are designed individually by the RNPC® dieticians by use of an in-house nutrition-calculation software (RNPC PILOT®).

2.3. Patients

The majority of the patients in the program were referred to the RNPC® program by their physicians, because of overweight or obesity while having at least one body weight-related co-morbidity. However, patients could also join the program without being directly referred by their physician. For instance this could be through word of mouth, flyers, or the RNPC® Internet site, followed by a written consent from the patient's physician. Blood analyses, with at least an evaluation of renal function, and an evaluation of pathologies and pharmaceutical treatments of the patient by the physician, were also mandatory to be enrolled in the program.

2.4. Measurements and calculations

Body weight and body fat percentage were measured at baseline, as well as at each follow-up visit at the dieticians by use of a calibrated bioelectrical impedance scale (Beurer BG42, Ulm, Germany). The percentage of body weight lost as fat-free mass was calculated as: (Δfat-free mass/Δweight) x 100%. Height was measured to the nearest cm at baseline using a height gauge. Body mass index (BMI) was calculated with the formula: body weight [kg]/(height [m])^2. Waist circumference (WC) was measured to the nearest cm at the natural waist. However, for patients with abdominal adiposity with no visible natural waist, the measurement was taken at the level midway between the lowest rib and the iliac crest, approximately 2–5 cm above the navel.

A 12-h fasting blood sample was drawn at baseline and analyzed for

the content of glucose. The physicians were encouraged to order these blood analyses. Methods used for all blood sample analyses were all validated according to the general requirements defined by the NF EN ISO 15189 and NF EN ISO/IEC 17025 standards for routine blood sample analysis. All data was entered in MySQL 5.7 database, and the database was managed by the IT consultant company Oriolis (Villeurbanne, France).

According to the RNPC® program, drop-out was evident when a patient did not return to counselling and measurement within 3 months since last counselling and measurement. We applied the same 3-month criteria to determine drop-out rates in this study. Two alternative options for a patient were possible; either the patient had completed the program or else the patient was ongoing in the program, but had not yet completed it. We determined both drop-out and ongoing rates, and the results are based on the patients who completed the weight loss phase and the patients who completed the weight stabilization phase, respectively. We did not consider potential data from the weight maintenance phase, as these measurements was carried out sporadically among a sample likely to be non-representative for the entire patient population. There was no exclusion criteria based on medications or medical conditions; however, protein intake was reduced among patients with poor renal function according to the recommendations from the Haute Autorité de Santé. The only exclusion criterion was pregnancy. Furthermore, we excluded patients with an age < 18 years and a baseline BMI < 25 or waist circumference < 80 cm for women and < 94 cm for men from the current analyses. Finally, the current analysis only included the first weight loss and subsequent weight stabilization cycle of each patient.

In the analyses of potential predictors for successful weight loss and weight loss maintenance, the patients were stratified according to gender and according to baseline fasting plasma glucose (FPG) levels i.e. normoglycemic (< 90 mg/dL and 90 to < 100 mg/dL), prediabetic (≥100 to < 115 mg/dL and ≥115 to ≤125 mg/dL) or diabetic (> 125 mg/dL) as pre-treatment FPG was recently shown to determine weight loss and weight loss maintenance success to diets varying in macronutrient composition and fiber content (Hjorth et al., 2017, 2018).

2.5. Statistical methods

Baseline characteristics were summarized as mean ± standard deviation (SD), median (interquartile range [IQR]), or as proportions. Differences in baseline characteristics between patients dropping out or not as well as genders were assessed using two-sample t-tests (variables possibly transformed before analysis) or Pearson's chi-squared tests.

Univariate linear mixed models were used to test the association between several baseline characteristics and change in weight from baseline to the end of the weight loss phase (with RNPC site as random effect) as well as to the end of the last stabilization phase (with subjects and RNPC site as random effects). Selected models were in subsequent models adjusted for a number of covariates.

Estimated mean body weight with 95% confidence intervals for both genders separately was analyzed by means of linear mixed models using all available weight measurements (also from non-completers). The linear mixed models included the two-way interaction between genders and time strata as well as both nested main effects and comprised additional fixed effects including baseline BMI, age, as well as random effects for subjects and RNPC site. Same model was used to estimate mean waist circumference with 95% confidence intervals. The level of significance was set at $P < 0.05$ and statistical analyses were conducted using STATA/SE 14.1 (Houston, USA).

Table 1
Baseline characteristics among patients starting on the RNPC® program stratified by gender.

	Women		Men		P-value
	N	% of n/mean (SD)/median (IQR)	n	% of n/mean (SD)/median (IQR)	
Smoking	9166	19.3%	3013	20.2%	0.29
Hypertension treatment	9166	6.2%	3013	9.8%	< 0.001
Diabetes treatment	9166	1.6%	3013	3.4%	< 0.001
Age (years)	9165	53.7 (14.2)	3013	55.8 (13.2)	< 0.001
Body weight (kg)	9166	84.8 (76.0; 96.1)	3013	104.7 (95.0; 116.8)	< 0.001
Height (cm)	9097	163 (6)	2985	176 (7)	< 0.001
Waist circumference (cm)	9133	103 (96; 113)	2998	116 (109; 125)	< 0.001
Body mass index (kg/m^2)	9097	32.2 (29.0; 36.1)	2985	34.0 (31.1; 37.4)	< 0.001
Fat mass (%)	8740	41.2 (4.8)	2842	37.2 (4.5)	< 0.001
Fasting glucose (mg/dL)	6130	96 (89; 105)	1969	103 (95; 115)	< 0.001

Analyzed by t-tests (numerical data; possibly transformed before analysis) or chi^2-tests (categorical data).

3. Results

3.1. Patients

12179 patients were included at baseline, of these 9166 (75%) were women and 3013 (25%) were men. Baseline characteristics of the included patients are shown in Table 1. A total of 1318 patients (11%) dropped out during the weight-loss phase, 52 patients (0.4%) had no measurement at termination of the weight-loss phase despite continuing in the program and 10809 of the patients (89%) completed the weight-loss phase. A total of 4525 patients (37%) did not continue after completing the weight-loss phase while 335 patients (3%) were still ongoing in the weight stabilization phase resulting in 6001 (49%) patients either completing or dropping out during the weight stabilization phase. In total, 2996 patients (25%) completed the weight stabilization phase (see Fig. 1).

No difference in dropout during the weight loss phase was found between genders ($P = 0.43$) or according to baseline weight ($P = 0.92$), BMI ($P = 0.23$), or age ($P = 0.13$). In contrary, among the 12179 patients starting the program, a larger proportion of the patients completing the weight stabilization phase were men (27% vs. 24%), had a 4.3 (3.6; 5.0) kg lower baseline bodyweight, a 1.6 (1.4–1.8) unit lower BMI and were 1.7 (1.0; 2.4) years older (all $P < 0.001$).

3.2. Weight loss and weight loss maintenance

The median weight loss and weight loss percentage during the weight loss period were 7.9 kg (IQR: 4.4; 12.3) and 10.6% (IQR: 5.6; 16.4) in women (n = 8123), and 10.3 kg (IQR: 6.0; 15.4) and 11.0% (6.3; 16.8) in men (n = 2686). The median duration of the weight loss phase was 111 days (IQR: 57; 182) in women and 92 days (IQR: 48; 157) in men. At completion of the weight stabilization phases median weight loss and weight loss percentage were 12.2 kg (IQR: 8.9; 16.5) and 17.7% (IQR: 12.8; 24.5) in women (n = 2172, obs = 2250) and 14.5 kg (IQR: 10.5; 20.2) and 16.9% (IQR: 12.4; 23.2) in men (n = 824, obs = 855). The median for the full program was 258 days (IQR: 196; 362) for women and 230 days (IQR: 167; 318) for men. The weight loss curve for the full program is shown in Fig. 2.

During the weight loss phase, patients (n = 2981) who later completed the weight stabilization phases lost 12.4 kg (13.6%) of their body weight, while those who did not complete the weight stabilization

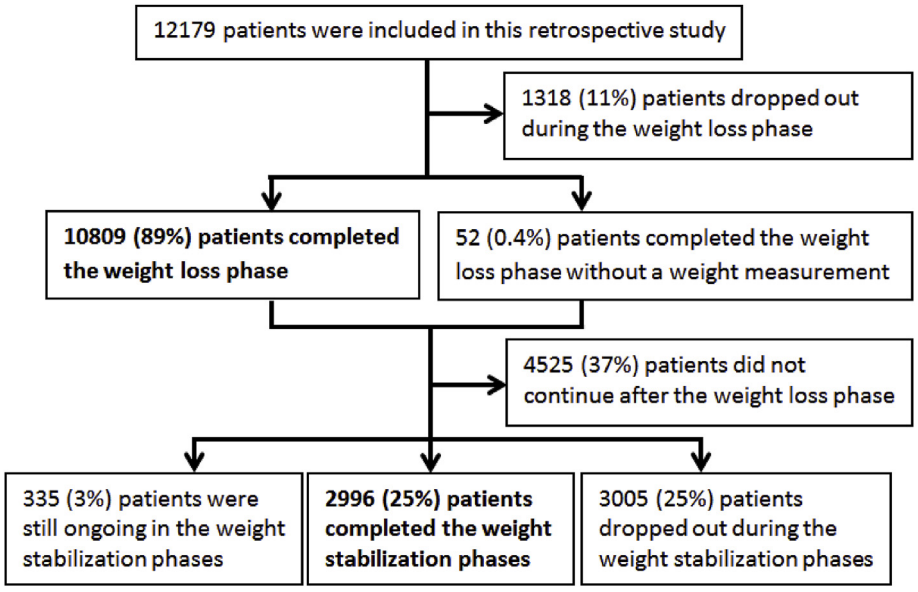

Fig. 1. Participant flow diagram.

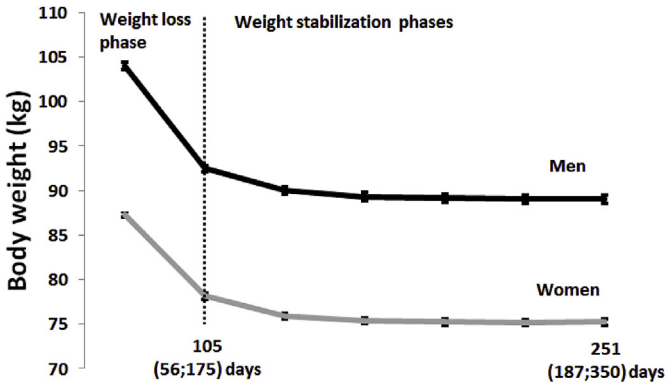

Fig. 2. Body weight during the RNPC® program stratified by gender. Data are presented as estimated mean body weight with 95% confidence intervals for each combination of the time-gender strata interaction in the linear mixed models, which were additionally adjusted for baseline BMI and age as fixed effects as well as subjects and RNPC site as random effects. The median (IQR) number of days is presented at completion of the weight loss phase [105 days (56; 175)] and weight stabilization phases [251 days (187; 350)]. Patients initiating the program (women: 9166; men: 3013), completing the weight loss phase (women: 8123; men: 2686), and completing the weight stabilization phases (women: 2172; men: 824).

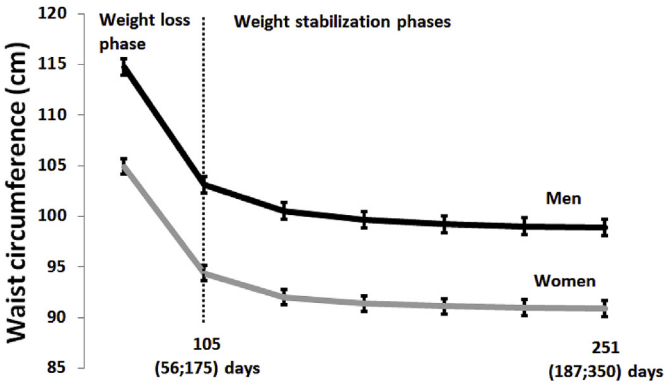

Fig. 3. Waist circumference during the RNPC® program stratified by gender. Data are presented as estimated mean waist circumference with 95% confidence intervals for each combination of the time-gender strata interaction in the linear mixed models, which were additionally adjusted for baseline BMI and age as fixed effects as well as subjects and RNPC site as random effects. The median (IQR) number of days is presented at completion of the weight loss phase [105 days (56; 175)] and weight stabilization phases [251 days (187; 350)]. Patients initiating the program (women: 9133; men: 2998), completing the weight loss phase (women: 8030; men: 2643), and completing the weight stabilization phases women: 2157; men: 814).

phases (n = 7492) lost 8.8 kg (9.1%). Therefore, patients completing the entire program lost 3.9 kg and 4.7% more of their initial body weight (both P < 0.001) during the weight loss phase compared to those completing the weight loss phase but not the weight stabilization phases.

3.3. Waist circumference

The median reduction in waist circumference during the weight-loss phase was 10 cm (IQR: 6; 14, n = 8030) in women and 11 cm (IQR: 7; 16, n = 2643) in men. At completion of the stabilization phases, the median reduction in waist circumference were 14 cm (IQR: 11; 19, n = 2157, obs = 2235) in women, and 16 cm (IQR: 12; 21, n = 814, obs = 845) in men. The change in waist circumference for the full program is shown in Fig. 3.

During the weight loss phase, patients (n = 2974) who later completed the weight stabilization phases reduced their waist circumference by 13.1 cm (12.2%) while those who did not complete the weight stabilization phases (n = 7368) reduced their waist circumference by 9.7 cm (8.8%). Therefore, patients completing the entire program reduced their waist circumference by 3.5 cm and 3.4% more (both P < 0.001) during the weight loss phase compared to those completing the weight loss phase but not the weight stabilization phases.

3.4. Body composition

The median percentage of body weight lost as fat-free mass during the weight loss period was 38.9% (IQR: 29.5; 41.7, n = 7429) in women and 39.3% (IQR: 35.2; 41.7, n = 2406) in men. During the stabilization phases, these numbers were 39.2% (32.4; 41.1, n = 2002, obs = 2072) in women and 39.2% (36.9; 40.8, n = 749, obs = 779) in men.

Table 2
Potential determinants for weight loss and weight loss maintenance.

	n `10,809	Weight loss phase	P-value	n 2,996[a]	Weight loss + stabilization phase	P-value
Gender	10,809			2996		
Women	8123	Reference		2172	Reference	
Men	2686	−2.39 (−2.68; −2.09)	< 0.001	824	- 2.62 (−3.21; −2.03)	< 0.001
Age (year)	10,808	0.037 (0.027; 0.046)	< 0.001	2996	0.053 (0.033; 0.073)	< 0.001
Body mass index (kg/m^2)	10,747	−0.56 (−0.58; −0.54)	< 0.001	2991	−0.88 (−0.93; −0.83)	< 0.001
Body weight (kg)	10,809	−0.18 (−0.18; −0.17)	< 0.001	2996	−0.26 (−0.27; −0.24)	< 0.001
Fat mass (%)	10,304	−0.29 (−0.32;-0.26)	< 0.001	2892	−0.45 (−0.51;-0.39)	< 0.001
Fat mass (kg)	10,304	−0.32 (−0.34;-0.31)	< 0.001	2892	−0.51 (−0.54;-0.48)	< 0.001
Fat free mass (kg)	10,304	−0.26 (−0.27;-0.25)	< 0.001	2892	−0.34 (−0.37;-0.32)	< 0.001
Waist circumference (cm)	10,776	−0.20 (−0.20; −0.19)	< 0.001	2992	−0.28 (−0.29; −0.26)	< 0.001
Baseline fasting glucose	7241			2186		
< 90 mg/dl	1873	Reference		588	Reference	
90 to < 100 mg/dl	2258	−0.41 (−0.83; 0.01)	0.056	672	−0.22 (−1.04; 0.61)	0.60
≥100–115 mg/dl	2080	−1.40 (−1.83;-0.97)	< 0.001	670	−1.42 (−2.25; −0.59)	< 0.001
> 115–125 mg/dl	420	−1.62 (−2.35; −0.89)	< 0.001	118	−1.96 (−3.44; −0.48)	0.009
> 125 mg/dl	610	−1.48 (−2.11;-0.85)	< 0.001	138	−1.73 (−3.11; −0.35)	0.014

Univariate linear mixed models were used to test the association between the baseline characteristics and change in weight during the weight loss phase (with site as random effect) as well during the entire program (with subjects and RNPC site as random effects).

[a] As the RNPC® program is a dynamic program allowing patients to relapse to an earlier energy level of their program patients could have more than one measurement at the final weight stabilization phase. The 2996 patients were observed 3105 times at this visit.

3.5. Weight loss predictors

In the univariate models, baseline age, various body composition measures and FPG as well as gender all predicted weight loss and weight loss maintenance success (all P < 0.001) (see Table 2). The association between baseline FPG and weight loss (during the weight loss phase) remained the same after adjusted for age and gender, however, the larger weight loss observed among patients with pre-diabetes and diabetes in the univariate analysis disappeared after additionally adjusting for baseline BMI [< 90 mg/dl: Reference; 90 to < 100 mg/dl: −0.06 (−0.44; 0.33, P = 0.78); ≥100–115 mg/dl: −0.36 (−0.78; 0.05, P = 0.085); > 115–125 mg/dl: 0.34 (−0.34; 1.03, P = 0.33); > 125 mg/dl: 0.79 (0.18; 1.40, P = 0.011)]. The same phenomenon was observed when evaluating the entire program (weight loss + stabilization phases) [< 90 mg/dl: Reference; 90 to < 100 mg/dl: −0.16 (−0.84; 0.53, P = 0.66); ≥100–115 mg/dl: −0.19 (−0.92; 0.53, P = 0.60); > 115–125 mg/dl: 0.23 (−1.04; 1.49, P = 0.73); > 125 mg/dl: 1.42 (0.20; 2.63, P = 0.022)].

4. Discussion

The RNPC® program is effective for both weight loss and long-term weight loss maintenance. A median 11% of initial body weight was lost among the 89% patients that completed the weight loss period with a median duration of 15 weeks. Approximately half of the initial sample started on the weight stabilization phases of which half (25% of initial sample) completed with a median 17% of initial body weight lost during the entire program with a median duration of approximately 36 weeks. A median of more than 60% of initial body weight was lost as fat mass during both the weight loss and weight stabilization phases. Hence, there was no detrimental effect on body composition.

Several commercial weight loss programs exist, and the effectiveness of these has previously been reviewed (Gudzune et al., 2015). It was concluded that an average 2.6–4.9% higher loss of initial body weight could be achieved after 12-months with the Jenny Craig® and Weight Watchers®[1] programs compared to control (education). The weight loss results obtained with the RNPC® program are more similar to what clinical research protocols report using very-low or low-calorie diets (Johansson et al., 2013). In general, weight loss programs with a high number of counselling sessions (≥1 per month) has been shown to produce greater weight loss and, more importantly, a better weight loss maintenance than programs with a low number of counselling sessions (Sacks et al., 2009; Voils et al., 2017; LeBlanc et al., 2011). The RNPC® program encouraged visits at the RNPC® clinics twice a month during weight loss and throughout the weight stabilization phases. The high frequency of visits may partly explain the higher weight loss rate in the RNPC® program compared to other weight loss programs (Gudzune et al., 2015).

The use of meal replacements or meal substitutes as a part of a structured meal plan was previously shown to be a safe and effective method for increasing dietary compliance and hence leading to a clinically relevant weight loss (Heymsfield et al., 2003). Also, meal replacements for weight loss are generally more easily managed compared to a normal weight loss diet regimen (Davis et al., 2010). Furthermore, in the RNPC® program, the RNPC® meal supplements served as an alternative to the high-GI carbohydrate and energy dense foods which were excluded from the diet during the program. Hence, in addition to supporting the desired macronutrient composition, especially by being high in proteins and fibers, the supplements supported the adherence and manageability of the weight loss and weight maintenance diet during the program.

Evidence supports that high-protein diets may be advantageous during weight loss and weight loss maintenance (Liu et al., 2015). A high-protein diet is known to reduce appetite and *ad libitum* energy intake (Belza et al., 2013). Also, in type 2 diabetics, shorter term (< 6 months duration) high-protein diets caused beneficial effects on weight loss, HbA1c levels and blood pressure (Dong et al., 2013). Also, a meta-analysis of longer-term studies (≥12 month duration) with high-protein low-carbohydrate diets concluded that the short term benefits of high-protein diets appear to persist at least partially long term, and that the benefits are greater with high dietary compliance (Clifton et al., 2014).

The importance of GI for weight loss has also been studied in a large 6-month study (Juanola-Falgarona et al., 2014). A moderate-carbohydrate low-GI diet was found more effective than a low-fat high-GI diet for reduction of body weight and control of glucose and insulin metabolism in overweight and obese adults. Another study compared three weight loss maintenance diets; low-fat (20% fats, 60% carbohydrates, 20% proteins), low-GI (40% fats, 40% carbohydrates, 20% proteins), and very low-carbohydrate (60% fats, 10% carbohydrates, 30% proteins) (Ebbeling et al., 2012). It was concluded that the low-GI diet had qualitatively similar benefits on energy expenditure to the very low-carbohydrate diet compared to the low-fat diet, but had no deleterious effects on markers of physiological stress and chronic inflammation as observed with the very low-carbohydrate diet. This suggests that reduction of dietary glycemic load rather than dietary fat is favorable for

weight-loss maintenance. Furthermore, the effect on weight loss maintenance of diets with combinations of low- and high-protein and low- and high-GI carbohydrates compared to a control diet were investigated in the Diogenes study (Larsen et al., 2010). The best diet for weight loss maintenance was found to be the high-protein, low-GI diet. This diet approximates the diet recommended to the patients in the RNPC® program, and hence, may partly explain the successful weight maintenance among the patients completing the program.

The RNPC® program was found to support the maintenance of fat-free mass during the weight loss, and this may also be due to the high-protein diet. A meta-analysis of 20 randomized controlled trials on weight loss in older adults (> 50y), showed a greater retention of fat-free mass and a greater loss of fat mass in trials with high-protein diets (proteins > 25% of total energy intake) compared to trials with low-protein diets (Kim et al., 2016). Furthermore, according to previous weight-loss trials a minimum protein intake of 1.05 g/kg/d was required to achieve optimal retention of fat-free mass (Krieger et al., 2006). The planned daily protein intake during the weight loss phase of the RNPC® program was above this level, i.e.1.5 g protein/kg/d for men and 1.2 g protein/kg/d for women. In summary, the combination of a high-protein low-GI diet and counseling sessions twice monthly during the RNPC® program potentially explains the effectiveness of the program for weight loss in the short and longer term.

Traditionally, BMI has been the preferred measurement of body size, and commonly used to diagnose overweight and obesity. Waist circumference reflects abdominal adiposity (Ross et al., 1985; Pouliot et al., 1994), and has been suggested as a superior measurement to BMI for prediction of type 2 diabetes risk and CVD risk (Huxley et al., 2010; Elbassuoni, 2013; Coutinho et al., 2013). Overall, the relative risk of a CVD event increases by 2% for every 1 cm increase in WC (De Koning et al., 2007). The WC reduction of 10–11 cm during the weight loss phase and 14–16 cm during the weight stabilization phases of the RNPC® program, therefore, corresponds to a substantial diabetes and CVD risk reduction.

It is essential when evaluating the usefulness of different weight loss methods not only to consider their effectiveness but also their cost. The cost for the RNPC® program for the patients corresponds to the price of the meal supplements (2.5 €/psc), whereas the individual consultation is included in this price. During the weight loss phase, the price is ~7.5 €/d for women and ~10 €/d for men, and during the weight stabilization phases the average price is 3.75 €/d for women and 5 €/d for men. Hence, according to the median completion times determined for the weight loss and weight stabilization phases for the RNPC® cohort, the average price during the entire RNPC® program was 5.4 €/d for women and 7.0 €/d for men. In comparison, the user fee of The Weight Watchers®' program was 0.7 €/d (for 6 months subscription), which includes weekly group meetings and online support. However, no meal supplements are included in the Weight Watchers®' program. The cost of Jenny Craig® is 1.1 €/d for weekly individual consultations plus 12.55–19.25 €/d for the meals, that is an overall 13–20 €/d price. Importantly, no additional food should be bought by Jenny Craig® patients. The average cost of a freelance dietician in France is 40 € per visit, corresponding to a price of 2.67 €/d for the same frequency of dietician consultations as in the RNPC® program. Also, this price is without the meal supplements provided in the RNPC® program. An advantage of the RNPC® program, however, is the rapid decrease in the cost of the program, as the weight loss phase, which is the most expensive phase, is designed to be short. Then, the cost gradually decreases with the progressive transition to a normal weight maintenance diet without meal supplements. This supports the patients' to maintain their weight loss on longer term, and after completion of the program, the patients are encouraged to continue the consultations at the dieticians free of charge to maintain their motivation for weight maintenance.

As alternative to weight loss through lifestyle modification, new pharmaceuticals have recently entered the marked for weight loss (Khera et al., 2016). For instance, the GLP-1 analogues (e.g. Liraglutide) have been shown effective for long-term weight loss (le Roux et al., 2017). However, they have to be injected daily and are rather expensive. Furthermore, pharmaceuticals have side effects and do not focus on improving the behavior and lifestyle of the overweight/obese individuals. Moreover, the treatment may be life long, and hence, costs may not decline over time. Gastric surgery is likewise an option for very obese individuals, but the method is costly and frequently gives rise to complications or adverse effects. Furthermore, nutrient malabsorption is frequent and requires special lifelong dietary supplements to avoid deficiencies.

Recently, pretreatment FPG was identified as a prognostic marker of weight loss during periods of characterized dietary composition. Specifically, the available research suggests that three groups of individuals representing normoglycemic, prediabetic and diabetic groups – may respond differently to different diets (Hjorth et al., 2017; Astrup and Hjorth, 2017). Normoglycemic individuals (FPG < 100 mg/dL) with overweight and obesity appear to benefit the most from low-fat high carbohydrate diets (Hjorth et al., 2017; Wan et al., 2017), prediabetics (FPG 100–125 mg/dL) may benefit most from increasing the amount of dietary fiber and reducing the glycemic index of the consumed carbohydrates (Hjorth et al., 2017, 2018), and individuals with FPG higher than 125 mg/dL (in many cases individuals with type 2 diabetes) should not only focus on the quality of the carbohydrates but also reduce total carbohydrates and increase dietary fat intake (Hjorth et al., 2017; Estruch et al., 2017). Normoglycemic individuals with FPG 90–100 mg/dL may also benefit from increasing fiber intake (Hjorth et al., 2018; Urban et al., 2017) and prediabetic individuals with FPG 115–125 mg/dL may have a benefit of increasing the amount of dietary fats on the expense of total and high glycemic index carbohydrates (Hjorth et al., 2017; Estruch et al., 2017). In our search of pretreatment determinants for weight loss during the RNPC® program, we identified gender, age, body size and body composition as well as FPG. From these univariate analyses the higher protein and lower GI diet appeared to work best in patients with prediabetes and diabetes. However, this association disappeared after adjusting for baseline BMI implying that baseline body size, known to affect both FPG and the ability to lose weight, is a confounder of the association between FPG and weight loss in the RNPC® program. The reason for baseline body size to be strongly associated with weight loss in the RNPC® program is likely due to patients with larger body size being encouraged to lose more weight. However, as pharmaceutical as well as dietary induced weight loss has generally been reported to be less efficient in patients with type 2 diabetes (Franz, 2007) this diet higher in protein and lower in GI seems as a dietary approach that works for diabetics (and prediabetes).

Strengths of the current study was its free living set-up in which we were able to test real-life efficacy of the novel RNPC® weight loss program in a very large sample size. Indeed we adapted a modified version of the best nutrient distribution for weight loss maintenance reported among 159 patients in the Diogenes study (Larsen et al., 2010) and tested this approach in several thousand patients. However, the lack of a control group prevented comparison with a non-RNPC® program group such as education or standard care. Therefore, in the discussion we compared the results from the RNPC® cohort with the absolute and percentage weight loss found in RCT testing other weight loss programs compared to controls. We observed a low drop-out rate during the weight loss phase (11%) but a large drop-out immediately after completing the weight loss phase (37%), as only ~50% continued on the weight stabilization phases. Roughly 50% of those continuing on the weight stabilization phases also completed. The reason for this relatively large drop-out after the weight loss phase and during the weight stabilization phases is uncertain. As the drop-out rates during the weight stabilization phase were unevenly distributed according to baseline BMI, age and gender, we adjusted for these parameters in our models. The 2996 participants who followed all the steps of the program initially lost more weight during the weight loss phase compared

to those not completing all phases of the program. Moreover, they continued to lose weight throughout and ended with an impressive 17% reduction of initial body weight in approximately 36 weeks. As these patients continued losing weight during the weight maintenance phases, the importance of following the entire program and not stopping after the weight loss phase should be highlighted. Furthermore, it has been shown that continuation of conditions that promote weight loss also promotes maintenance of this lower weight (Ross Middleton et al., 2012), highlighting the importance of maintaining regular visits to the RNPC® centers even after weight loss and stabilization have been achieved.

In conclusion, the RNPC® program is cost-effective and well tolerated for short-term body weight loss as 89% of patients completed the ~15-week weight loss phase with a median 11% of initial body weight lost. For unknown reasons, drop-out rates were high before and during the weight stabilization phases and only 25% completed the entire ~36-week program. However, among the patients completing, the program was highly effective and resulted in a 17% reduction of initial body weight. The program was particularly effective among patient with elevated fasting plasma glucose although likely to have been confounded by baseline body size.

Author contributions

MFH, RL, and AA conceived the idea of the current analysis. TKT and MFH analyzed the data and wrote the first draft of the paper. All authors have reviewed the manuscript critically and approved the final manuscript.

Disclosure

AA is consultant for Groupe Éthique et Santé, and chairman of their scientific advisory board. He is consultant or member of advisory boards for Dutch Beer Institute, NL, Feast Kitchen A/S, DK, McCain Foods Limited, USA, Nestlé Research Center, Switzerland, Weight Watchers, USA; Gelesis, USA, BioCare Copenhagen, Zaluvida, Switzerland, Basic Research, USA, Beachbody, USA, Novo Nordisk, DK, Saniona, DK, & Scandinavian Airlines System, DK. Current research is in part funded by grants from Arla Foods, DK, Danish Dairy Research Council, & Gelesis, USA. AA is co-author of a number of diet/cookery books, including personalized nutrition for weight loss, published in several languages. He is co-owner and member of the Board of the consultancy company Dentacom Aps, co-founder and co-owner of UCPH spin-out companies Mobile Fitness A/S, Flaxslim ApS, and Personalized Weight Management Research Consortium ApS (Gluco-diet.dk).

MFH reports grants from Groupe Éthique et Santé and Gelesis (USA) during the conduct of the study. In addition, MFH is co-inventor on a pending provisional patent application on the use of biomarkers for prediction of weight-loss responses (with University of Copenhagen & Gelesis, USA), he is co-author of 2 diet/cookery books regarding personalized nutrition for weight loss, and co-owner of UCPH spin-out company “Personalized Weight Management Research Consortium ApS (Gluco-diet.dk)”.

OF is employed at the Groupe Éthique et Santé. RL is CEO and founder of Groupe Éthique et Santé, and TKT reports grants from Groupe Éthique et Santé during the conduct of the study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.obmed.2018.05.001.

References

Astrup, A., Hjorth, M.F., 2017. Low-fat or low carb for weight loss? it depends on your glucose metabolism. EBioMedicine 22, 20–21.

Belza, A., Ritz, C., Sorensen, M.Q., Holst, J.J., Rehfeld, J.F., Astrup, A., 2013. Contribution of gastroenteropancreatic appetite hormones to protein-induced satiety. Am. J. Clin. Nutr. 97, 980–989.

Black, A.E., Coward, W.A., Cole, T.J., Prentice, A.M., 1996. Human energy expenditure in affluent societies: an analysis of 574 doubly-labelled water measurements. Eur. J. Clin. Nutr. 50, 72–92.

Clifton, P.M., Condo, D., Keogh, J.B., 2014. Long term weight maintenance after advice to consume low carbohydrate, higher protein diets–a systematic review and meta analysis. Nutr. Metabol. Cardiovasc. Dis. 24, 224–235.

Coutinho, T., Goel, K., De Sá, D.C., Carter, R.E., Hodge, D.O., Kragelund, C., et al., 2013. Combining body mass index with measures of central obesity in the assessment of mortality in subjects with coronary disease: role of “normal weight central obesity”. J. Am. Coll. Cardiol. 61, 553–560.

Davis, L.M., Coleman, C., Kiel, J., Rampolla, J., Hutchisen, T., Ford, L., et al., 2010. Efficacy of a meal replacement diet plan compared to a food-based diet plan after a period of weight loss and weight maintenance: a randomized controlled trial. Nutr. J. 9, 11.

De Koning, L., Merchant, A.T., Pogue, J., Anand, S.S., 2007. Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: meta-regression analysis of prospective studies. Eur. Heart J. 28, 850–856.

Dong, J., Zhang, Z., Wang, P., Qin, L., 2013. Effects of high-protein diets on body weight, glycaemic control, blood lipids and blood pressure in type 2 diabetes: meta-analysis of randomised controlled trials. Br. J. Nutr. 110, 781–789.

Ebbeling, C.B., Swain, J.F., Feldman, H.A., Wong, W.W., Hachey, D.L., Garcia-Lago, E., et al., 2012. Effects of dietary composition on energy expenditure during weight-loss maintenance. J. Am. Med. Assoc. 307, 2627–2634.

EFSA Panel on Dietetic Products Nutrition and Allergies (NDA), 2015. Statement on the conditions of use for health claims related to meal replacements for weight control. EFSA J. 13, 4287.

Elbassuoni, E., 2013. Better association of waist circumference with insulin resistance and some cardiovascular risk factors than body mass index. Endocr. Regul. 47, 3–14.

Estruch, Ramon, Corella, Dolores, Salas-Salvado, Jordi, Hjorth, Mads F., Astrup, Arne, Zohar, Yishai, Urban, Lorien E., Serra-Majem, Lluis, Lapetra, José, Aros, Fernando, Fiol, Miquel, Gomez-Gracia, Enrique, Martinez-Gonzalez, Miguel A., Fito, Montserrat, Ros, Emilio, 2017. Pretreatment Fasting Plasma Glucose Determines Weight Loss on High-fat Diets: the Predimed Study. https://ada.scientificposters.com/epsAbstractADA.cfm?id=3.

Franz, M.J., 2007. The dilemma of weight loss in diabetes. Diabetes Spectr. 20, 133–136.

Gudzune, K.A., Bleich, S.N., Clark, J.M., 2015. Efficacy of commercial weight-loss programs. Ann. Intern. Med. 163, 399.

Heymsfield, S., Van Mierlo, C., Van der Knaap, H., Heo, M., Frier, H., 2003. Weight management using a meal replacement strategy: meta and pooling analysis from six studies. Int. J. Obes. 27, 537–549.

Hjorth, M.F., Ritz, C., Blaak, E.E., Saris, W.H., Langin, D., Poulsen, S.K., et al., 2017. Pretreatment fasting plasma glucose and insulin modify dietary weight loss success: results from 3 randomized clinical trials. Am. J. Clin. Nutr. 106, 499–505.

Hjorth, M.F., Due, A., Larsen, T.M., Astrup, A., 2017. Pre-treatment fasting plasma glucose modifies dietary weight loss maintenance success: results from a stratified RCT. Obesity 25, 2045–2048.

Huxley, R., Mendis, S., Zheleznyakov, E., Reddy, S., Chan, J., 2010. Body mass index, waist circumference and waist: hip ratio as predictors of cardiovascular risk—a review of the literature. Eur. J. Clin. Nutr. 64, 16–22.

Johansson, K., Neovius, M., Hemmingsson, E., 2013. Effects of anti-obesity drugs, diet, and exercise on weight-loss maintenance after a very-low-calorie diet or low-calorie diet: a systematic review and meta-analysis of randomized controlled trials. Am. J. Clin. Nutr. 99, 14–23.

Juanola-Falgarona, M., Salas-Salvado, J., Ibarrola-Jurado, N., Rabassa-Soler, A., Diaz-Lopez, A., Guasch-Ferre, M., et al., 2014. Effect of the glycemic index of the diet on weight loss, modulation of satiety, inflammation, and other metabolic risk factors: a randomized controlled trial. Am. J. Clin. Nutr. 100, 27–35.

Khera, R., Murad, M.H., Chandar, A.K., Dulai, P.S., Wang, Z., Prokop, L.J., et al., 2016. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. J. Am. Med. Assoc. 315, 2424–2434.

Kim, J.E., O'Connor, L.E., Sands, L.P., Slebodnik, M.B., Campbell, W.W., 2016. Effects of dietary protein intake on body composition changes after weight loss in older adults: a systematic review and meta-analysis. Nutr. Rev. 74, 210–224.

Krieger, J.W., Sitren, H.S., Daniels, M.J., Langkamp-Henken, B., 2006. Effects of variation in protein and carbohydrate intake on body mass and composition during energy restriction: a meta-regression 1. Am. J. Clin. Nutr. 83, 260–274.

Larsen, T.M., Dalskov, S., van Baak, M., Jebb, S.A., Papadaki, A., Pfeiffer, A.F., et al., 2010. Diets with high or low protein content and glycemic index for weight-loss maintenance. N. Engl. J. Med. 363, 2102–2113.

le Roux, C.W., Astrup, A., Fujioka, K., Greenway, F., Lau, D.C., Van Gaal, L., et al., 2017. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet 389, 1399–1409.

LeBlanc E., O'Connor E., Whitlock E.P., Patnode C., Kapka T.. 2011.

Liu, A.Y., Silvestre, M.P., Poppitt, S.D., 2015. Prevention of type 2 diabetes through lifestyle modification: is there a role for higher-protein diets? Adv Nutr. 6, 665–673.

Pouliot, M., Després, J., Lemieux, S., Moorjani, S., Bouchard, C., Tremblay, A., et al., 1994. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am. J. Cardiol. 73, 460–468.

Ross, R., Leger, L., Morris, D., de Guise, J., Guardo, R., 1985. Quantification of adipose tissue by MRI: relationship with anthropometric variables. J. Appl. Physiol. 1992

(72), 787–795.
Ross Middleton, K., Patidar, S., Perri, M., 2012. The impact of extended care on the long-term maintenance of weight loss: a systematic review and meta-analysis. Obes. Rev. 13, 509–517.
Sacks, F.M., Bray, G.A., Carey, V.J., Smith, S.R., Ryan, D.H., Anton, S.D., et al., 2009. Comparison of weight-loss diets with different compositions of fat, protein, and carbohydrates. N. Engl. J. Med. 360, 859–873.
Sawamoto, R., Nozaki, T., Nishihara, T., Furukawa, T., Hata, T., Komaki, G., et al., 2017. Predictors of successful long-term weight loss maintenance: a two-year follow-up. Biopsychosoc. Med. 11, 14.
Skov, A., Toubro, S., Rønn, B., Holm, L., Astrup, A., 1999. Randomized trial on protein vs carbohydrate in ad libitum fat reduced diet for the treatment of obesity. Int. J. Obes. Relat. Metab. Disord. 23.
Unick, J.L., Hogan, P.E., Neiberg, R.H., Cheskin, L.J., Dutton, G.R., Evans-Hudnall, G., et al., 2014. Evaluation of early weight loss thresholds for identifying nonresponders to an intensive lifestyle intervention. Obesity 22, 1608–1616.
Urban, Lorien E., Roberts, Susan B., Zohar, Yishai, Astrup, Arne, Fiil Hjorth, Mads, Pittas, Anastassios G., Krupa Das, Sai, 2017. Pretreatment Fasting Glucose Concentration Predicts Weight Loss on a High-fiber, Low Glycemic Load Diet: the Healthy Weight for Living Study. https://ada.scientificposters.com/epsAbstractADA.cfm?id=2.
Voils, C.I., Olsen, M.K., Gierisch, J.M., Mcvay, M.A., Grubber, J.M., Gaillard, L., et al., 2017. Maintenance of weight loss after initiation of nutrition TrainingA randomized TrialWeight loss maintenance intervention. Ann. Intern. Med. 166, 463–471.
Wan, Y., Wang, F., Yuan, J., Li, J., Jiang, D., Zhang, J., et al., 2017. Effects of macro-nutrient distribution on weight and related cardiometabolic profile in healthy non-obese Chinese: a 6-month, randomized controlled-feeding trial. EBioMedicine 22, 200–207.
WHO, 2000. Obesity: Preventing and Managing the Global Epidemic.
WHO, 2009. Global Health Risks: Mortality and Burden of Disease Attributable to Selected Major Risks.
WHO, 2017. Obesity and Overweight.
Wing, R.R., Phelan, S., 2005. Long-term weight loss maintenance. Am. J. Clin. Nutr. 82, 222S–225S.